Original Article

Detection of Sentinel Lymph Nodes in Patients with Papillary Thyroid Cancer

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OBJECTIVES: To determine the feasibility of sentinel lymph node biopsy as a means of evaluating the cervical lymph nodes of patients with papillary thyroid cancer.

METHODS: Isosulfan blue dye was injected around the tumour of 68 patients with papillary thyroid cancer; sentinel lymph node biopsy was performed in addition to subtotal thyroidectomy and central and modified lateral neck lymph node dissections. Surgical specimens were examined by routine processing to determine whether metastasis was present.

RESULTS: Sentinel lymph nodes were identified in 63 (92.6%) of the 68 patients. There was concordance between the sentinel lymph node status and the final regional lymph node status in 58 (92.1%) of the 63 patients. There were five false-negative cases. Sentinel lymph node biopsy had a sensitivity of 87.5% (35/40), specificity of 100% (23/23), positive predictive value of 100% (35/35), negative predictive value of 82.1% (23/28), and accuracy of 92.1% (58/63).

CONCLUSIONS: Sentinel lymph node biopsy may allow discrimination between patients with true lymph-node-negative papillary thyroid carcinoma and those with non-palpable metastatic lymph nodes. It may also be helpful in diagnosing metastases and avoiding unnecessary lymph node dissection in thyroid cancer. [*Asian J Surg* 2003;26(3):145–8]

Introduction

The proper management of potential occult lymph node metastasis in thyroid cancer remains a matter of controversy. Those who choose elective lymph node dissection insist that metastasis is found in 50% to 80% of patients with clinically negative lymph nodes, and that their removal reduces recurrence.[1] Opponents of this approach, while recognizing that metastasis may be present, maintain that routine dissection is unnecessary because the recurrence rate is only 1.4% and the 5-year mortality rate ranges from 0.9% to 17%.[2]

Most studies have shown that lymph node metastasis by thyroid cancer is not associated with increased mortality,[3] but others have found a statistically significant association between nodal metastasis and mortality in follicular cancer.[4,5] The effect of nodal metastasis on survival may often be outweighed by the benefits of age. When matched for age, the outcome of patients with nodal metastases was found to be significantly worse than that of patients who were nodal metastasis-free: 15% versus 41% among patients older than 40 years.[6] When controlled for other risk factors, such as older age and vascular invasion, several large retrospective studies have shown that lymph node metastasis is associated with an overall lower survival rate,[5,7,8] and this has led to the recommendation of elective lymph node dissection in well-differentiated thyroid cancer as a means of decreasing the recurrence rate and improving survival.[7] Although regional lymph node metastasis is associated with a mortality rate of 78% in high-risk groups,[9] lymphadenectomy has only been shown to have a significant benefit on the 20-year survival rate of the high-

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risk subgroup of patients with papillary thyroid cancer.[10]

The first lymph node that drains a primary tumour is referred to as the sentinel lymph node (SLN), and if lymphatic drainage occurs in a step-wise fashion, the SLN should reflect the pathological status of the remaining lymph node compartment. Routine adoption of prophylactic lymph node dissection is therefore not generally accepted as standard treatment for clinically occult nodal disease. The objectives of this study were to determine whether SLN biopsy (SLNB) in patients with papillary thyroid carcinoma is capable of discriminating true lymph-node-negative patients from those with non-palpable metastatic lymph nodes and whether SLNB could provide an alternative to elective lymph node dissection in patients with clinically occult lymph node metastasis.

Patients and methods

All patients with a preoperative diagnosis of papillary thyroid carcinoma by fine needle aspiration were eligible for the study. Exclusion criteria were cervical lymphadenopathy, complications of chronic thyroiditis or Graves' disease, and a previous history of neck surgery or irradiation. This study was approved by the University Ethics Board, and informed consent was obtained from all patients.

At surgery, the thyroid nodule was exposed by laterally retracting the sternohyoid muscle. A 27-gauge tuberculin syringe was used to inject 0.3 mL of isosulfan blue (Lymphazurin 1%, United States Surgical Corporation, Norwalk, CT, USA) at the 3 o'clock, 6 o'clock, 9 o'clock and 12 o'clock positions. The lymph node that stained first was presumed to be the SLN (Figure), and the blue lymphatic channels were traced to the central compartment and the lateral compartment. The SLN was sent to the pathology laboratory for preparation of both frozen and permanent sections. Several of the permanent sections from each SLN were stained with haematoxylin and eosin in the usual manner. Immunohistochemistry was not used in the assessment of the lymph nodes. Total lobectomy and partial resection of the contralateral lobe, so-called "subtotal thyroidectomy", was then performed, and central and modified ipsilateral lymph node dissections were routinely performed.

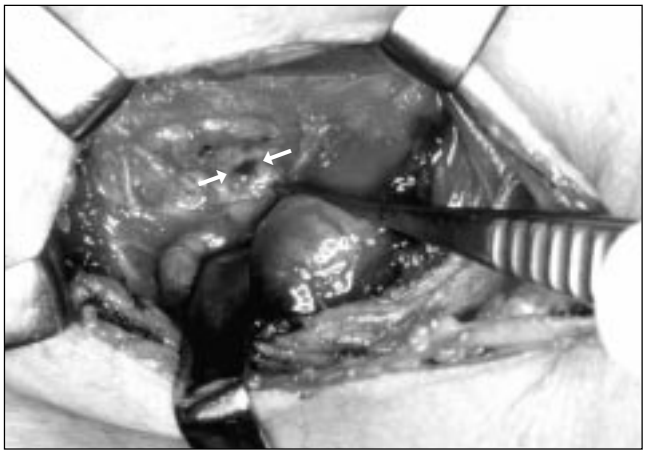

Figure. Isosulfan blue-stained sentinel lymph node (arrows) in the central compartment.

Results

A total of 68 patients were enlisted (60 females, 8 males; age range, 22–69 years; mean age, 42 years). Their primary tumours ranged between 0.6 cm and 3.9 cm (mean, 1.9 cm) in maximum diameter. All patients had a solitary palpable tumour and no palpable cervical lymphadenopathy before surgery.

SLNs were identified in 63 of the 68 patients (92.6%). An SLN was found in the central compartment in 59 of the 63 patients, in the lateral compartment in eight patients, and four patients had an SLN in both compartments according to the Classification of Thyroid Cancer, edited by the Japanese Society of Thyroid Surgery.[11] The mean number of SLNs identified was 2.02 ± 3.41. Some of the parathyroid glands were identified prior to the injection of isosulfan blue, but others were easily identified because they stained blue.

Thirty-five of the 63 patients (55.6%) had metastasis-positive SLNs, and 28 (44.4%) had metastasis-negative SLNs (Table). There was concordance between the SLN status and the final regional lymph node status in 58 of the 63 patients (92.1%). Five of the 63 patients had metastasis-negative SLNs but metastasis-positive regional lymph nodes. SLNB had 87.5% (35/40) sensitivity, 100% (23/23) specificity, 100% (35/35) positive predictive value, 82.1% (23/28) negative predictive value, and 92.1% (58/63) accuracy. There were no operative complications and no complications with the use of isosulfan blue.

Unlike some reports from Western countries, we had five false-negative cases. The false-negative rate for thyroid cancer in the West is unknown as modified neck dissection is not performed in every case.

Discussion

Lymph node metastases from well-differentiated thyroid cancers are associated with high regional recurrence rates. Surgical options consist of blind nodal sampling, "berry

Table. Pathological diagnosis of sentinel and regional lymph nodes

Sentinel lymph node metastases	Regional lymph node metastases	
	Positive n (%)	Negative n (%)
Positive	35 (55.6)	–
Negative	5 (7.9)	23 (36.5)

picking" procedures, elective lymph node dissection, and modified neck dissections.[12] SLNB was developed as an alternative to elective lymph node dissection for patients with clinically occult lymph node metastasis.

Kelemen et al described the first use of SLNB for thyroid carcinoma.[13] These authors identified SLNs in 12 of 12 patients with thyroid cancer; five SLNs were positive for thyroid carcinoma. Central neck dissection alone was performed in these five patients, and the SLN was the only tumour-bearing lymph node in two of the cases. Haigh and Giuliano performed SLNB in 17 thyroid cancers.[14] One SLN failed to show metastasis, but metastases were identified in nine (56%) of the remaining 16 patients. However, as central neck dissections were not performed after SLNB in all of the patients in these two studies, the false-negative rate is unknown.

Complete central neck dissection should be performed in patients whose lymph nodes are negative, as well as in patients whose lymph nodes are positive. Dixon et al reported identifying SLNs in 10 of 12 patients with papillary cancer;[15] six had true-positive SLNs, two had true-negative SLNs, and two had false-negative SLNs (according to the results of node dissection in one case and of lateral uptake on ^{131}I scanning in the other). Pelizzo et al identified SLNs in 22 of 29 patients, and detected neoplastic involvement in four of the 22 cases.[16] Among the 18 patients whose SLNs were not metastatic, the other nodes were also disease-free. In two of the seven patients in whom SLNs were not identified by the staining procedure, metastatic nodes were detected in the central compartment. The authors performed total thyroidectomy and lymph node dissection of the central and lateral compartments in all of the 29 patients. Arch-Ferrer et al identified SLNs in 20 of 22 patients with papillary thyroid carcinoma,[17] and the SLNs were positive in 12 of the 20 patients. Immunohistochemical analysis for CK-7 revealed micrometastases in five of the eight SLNs previously evaluated as negative by haematoxylin and eosin staining. One of the two patients in whom an SLN could not be identified had lymph node metastasis in the lateral compartment and the other was metastasis-free. Fukui et al reported a concordance between the SLN findings and the regional lymph node status in 19 of 21 patients with papillary thyroid cancer.[18] In two patients, the SLN was negative for metastasis, but the non-SLNs were positive. Their overall reliability rate of SLNB was 86%, so it was a good technique for estimating the status of cervical lymph nodes in patients with papillary thyroid carcinoma.

Scintigraphic localization of SLNs has been attempted in patients suspected of having thyroid cancer.[19] On the day of surgery, a technetium colloid was injected into the tumour. During surgery, the primary tumour was excised first, and then the SLNs were removed using a gamma probe. SLNs were detected in patients with papillary thyroid cancer, and there were no false-negative findings. Catarci et al used preoperative lymphoscintigraphy with 99mTc-labelled colloidal albumin, vital dye staining, and hand-held gamma probing in six patients diagnosed with papillary thyroid cancer.[20] They identified the SLN by these methods in all six cases (100%), with identification rates by preoperative lymphoscintigraphy, vital dye, and probe scanning of 66%, 50% and 83%, respectively.

The malignancy of Hürthle cell tumours of the thyroid is difficult to determine even during the final pathological examination, and nodal metastasis of Hürthle cell tumours has been described as a major indicator of mortality and morbidity.[21] SLNB may assist in the diagnosis of the malignancy of Hürthle cell tumours or atypical follicular tumours when there is no or questionable evidence of capsular or vascular invasion on frozen sections. If metastasis is identified in the sentinel node, then invasion can be presumed and total thyroidectomy performed, thereby avoiding a second operation.[14]

One of the benefits of SLN dissection may be the identification of SLNs outside the central neck that contain occult metastases of medullary thyroid carcinoma.[14] This would identify disease that would have been left unresected by central neck dissection alone, and provide a more logical approach to lateral neck dissection. SLN dissection may be superior to jugular node sampling in detecting residual nodal metastatic disease.

Although it continues to be a matter of controversy, ^{131}I ablation has been shown by some authors to decrease local recurrence and improve survival.[5] The efficacy of ^{131}I on survival of well-differentiated thyroid cancer has recently been questioned.[22] The selection of patients with metastatic disease would allow a more directed approach of ^{131}I ablation postoperatively and possibly help resolve this controversy. SLN sampling could be used to avoid ^{131}I ablation in patients with low-risk thyroid cancer whose SLN is negative.

We had three patients in whom an SLN was detected in the lateral compartment alone. Since our search for the SLN was only successful when the surgeon proceeded from the central compartment to explore the lateral compartment, it would seem that for mapping purposes, exploration should not be restricted to the lymph nodes of the central compartment.[16] As some SLNs are located outside the central compartment of the neck, SLNB for thyroid cancer must be performed outside the central compartment. The combination of vital dye staining and radiolymphoscintigraphy in thyroid cancer has increased the yield of SLNB. The advantage of lymphoscintigraphy with intraoperative gamma probe guidance is that the radiolabelled material is injected preoperatively, thereby eliminating disruption of the lymphatics during the initial dissection. Radioscintigraphy also allows for the diagnosis and identification of SLNs in patients whose SLN lies outside the central compartment. SLNB with intraoperative gamma probing is currently performed in our department.

Conclusion

The preliminary findings indicate that the SLN hypothesis may be applicable to thyroid cancer. SLNB may allow discrimination of true lymph-node-negative papillary thyroid carcinoma patients from those with non-palpable lymph nodes. It may also be helpful in diagnosing metastases and avoiding unnecessary lymph node dissection in thyroid cancer. Selective lymph node dissection not only lessens the chance of locoregional relapse but also the number of complications.

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